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Very Early Recurrence After Liver Resection for Intrahepatic Cholangiocarcinoma
Considering Alternative Treatment Approaches

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IMPORTANCE Although surgery offers the best chance of a potential cure for patients with localized, resectable intrahepatic cholangiocarcinoma (ICC), prognosis of patients remains dismal largely because of a high incidence of recurrence.

OBJECTIVE To predict very early recurrence (VER) (ie, recurrence within 6 months after surgery) following resection for ICC in the pre- and postoperative setting.

DESIGN, SETTING, AND PARTICIPANTS Patients who underwent curative-intent resection for ICC between May 1990 and July 2016 were identified from an international multi-institutional database. The study was conducted at The Ohio State University in collaboration with all other participating institutions. The data were analyzed in December 2019.

MAIN OUTCOMES AND MEASURES Two logistic regression models were constructed to predict VER based on pre- and postoperative variables. The final models were used to develop an online calculator to predict VER and the tool was internally and externally validated.

RESULTS Among 880 patients (median age, 59 years [interquartile range, 51-68 years]; 388 women [44.1%]; 428 [50.2%] white; 377 [44.3%] Asian; 27 [3.2%] black]), 196 (22.3%) developed VER. The 5-year overall survival among patients with and without VER was 8.9% vs 49.8%, respectively ($P < .001$). A preoperative model was able to stratify patients relative to the risk for VER: low risk (6-month recurrence-free survival [RFS], 87.7%), intermediate risk (6-month RFS, 72.3%), and high risk (6-month RFS, 49.5%) (log-rank $P < .001$). The postoperative model similarly identified discrete cohorts of patients based on probability for VER: low risk (6-month RFS, 90.0%), intermediate risk (6-month RFS, 73.1%), and high risk (6-month RFS, 48.5%) (log-rank, $P < .001$). The calibration and predictive accuracy of the pre- and postoperative models were good in the training (C index: preoperative, 0.710; postoperative, 0.722) as well as the internal (C index: preoperative, 0.715; postoperative, 0.728; bootstrapping resamples, n = 5000) and external (C index: postoperative, 0.672) validation data sets.

CONCLUSION AND RELEVANCE An easy-to-use online calculator was developed to help clinicians predict the chance of VER after curative-intent resection for ICC. The tool performed well on internal and external validation. This tool may help clinicians in the preoperative selection of patients for neoadjuvant therapy as well as during the postoperative period to inform surveillance strategies.

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Supplemental content

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Intrahepatic cholangiocarcinoma (ICC) ranks as the second most common primary liver malignancy, with a growing incidence in Western and Eastern countries over the past 3 decades.[1,2] Although surgery offers the best chance of a potential cure for patients with localized, resectable ICC, the prognosis of these patients is still discouraging, with a median overall survival (OS) ranging from 12 to 31 months.[3,4] In fact, 50% to 70% of patients with ICC will experience a recurrence following resection.[5,6]

Previous studies defined recurrence following resection for ICC as early vs late using a cutoff of 2 years.[5,6] Patients with early (<24 months) vs late recurrence (>24 months) had distinct recurrence patterns, predictors, and outcomes.[5,6] Patients with late recurrence generally had a better prognosis compared with patients who developed early recurrence following ICC resection.[5,7] In addition, certain tumor characteristics, including tumor size and tumor multifocality, were predominantly associated with early but not late recurrence.[5,7] Although such a categorization (ie, early [<24 months] vs late [>24 months]) aligns with previous studies on hepatocellular carcinoma (HCC),[8,9] it may not be appropriate for patients with ICC given that most recurrences occur within the first 2 years after resection of ICC.[5,6] In fact, a previous study from our own group noted that approximately one-quarter of patients with ICC had very early recurrence (VER) (ie, recurrence within 6 months after initial resection).[5] Patients with VER were even more common than individuals who experienced a late recurrence (>2 years).[5] As such, identifying patients who are at risk for VER is important to construct individualized surveillance strategies following resection for ICC or even recommend an alternative treatment strategy for these patients, including neoadjuvant therapy or other nonsurgical treatment modalities. To our knowledge, no predictive tool exists to predict VER among patients undergoing curative-intent liver resection for ICC. As such, the objective of this study was to characterize patients who develop VER following curative-intent resection for ICC. In addition, we sought to develop preoperative and postoperative models to predict VER based on factors known before and after surgery using a large, multi-institutional database. To facilitate the clinical applicability of the models, an easy-to-use online calculator was developed to predict the risk of VER among individuals with resectable ICC in the pre- and postoperative setting.

Key Points

Question Which patients will develop very early recurrence (VER) (ie, recurrence within 6 months) after resection for intrahepatic cholangiocarcinoma and are the best candidates for neoadjuvant chemotherapy?

Findings In this multi-institutional cohort study, 196 patients (22.3%) developed VER following resection with a detrimental association with overall survival (5-year overall survival, 8.9%). Two predictive models were developed to identify high-risk patients for VER in the pre- and postoperative setting with a good predictive accuracy in the training as well as the internal and external validation data sets.

Meaning These data emphasize that VER is common after intrahepatic cholangiocarcinoma resection and highlight the need for an alternative treatment approach (ie, neoadjuvant chemotherapy) for high-risk patients.

Methods

Patient Cohort and Data Collection

Patients who underwent liver resection for histologically proven ICC between May 1990 and July 2016 were identified in an international multi-institutional database that incorporated data from 15 major hepatobiliary institutions involved in the International Intrahepatic Cholangiocarcinoma Collaboration.[10-12] The VER of ICC was defined as the incidence of recurrence within 6 months after resection based on previous studies.[13-16] Only patients who received curative-intent hepatectomy were included in the analysis. Patients were excluded for (1) macroscopically positive surgical margins, (2) lack of follow-up data, and (3) death or loss to follow-up without any evidence of recurrence within 6 months following resection. The institutional review boards of all the participating facilities approved the study. Patient consent was waived as retrospective deidentified data were analyzed.

Clinicopathologic variables of patients with ICC extracted included age, sex, race, body mass index (calculated as weight in kilograms divided by height in meters squared), cirrhosis, American Society of Anesthesiologists class, preoperative serum levels of carcinoembryonic antigen and carbohydrate antigen (CA) 19-9, preoperative lymph node (LN) assessment, tumor size, tumor number, location, macro- or microvascular invasion, perineural invasion, American Joint Committee on Cancer (AJCC) tumor stage, AJCC N stage, tumor grade, morphological type (ie, mass-forming, intraductal growth, and periductal infiltrating), extent of resection, resection margin status, intraoperative blood loss, operative time, use of perioperative chemotherapy or radiotherapy, and postoperative complications.[5] Major hepatectomy was defined as resection of 3 or more Couinaud segments.[17] Macrovascular invasion was defined as invasion of the portal vein, hepatic artery, or hepatic veins, whereas microvascular invasion was defined as intraparenchymal vascular involvement identified on histology testing results.[18] Tumor stage was defined following the AJCC seventh edition staging manual.

After liver resection, patients were monitored for recurrence with serum tumor markers and imaging studies, including ultrasonography, computed tomography, and/or magnetic resonance imaging. In general, patients were followed up once every 3 to 4 months for the first 3 years, once every 6 months from years 4 to 5, and then annually.[19] Recurrence was defined as suspicious or positive findings on surveillance imaging or histologically confirmed disease. The treatment of tumor recurrence was decided following consensus among the multidisciplinary team in each institution.

Statistical Analysis

Categorical and continuous variables were presented as frequency (%) and median (interquartile range [IQR]), respec-

tively. The association of several clinicopathological factors with the incidence of VER following ICC resection was assessed by means of logistic regression analysis. Variables significant on bivariate analysis were subsequently included in the multivariable logistic regression model and a stepwise selection method was used (forward selection method using the lowest bayesian information criterion). Two risk scores to predict VER of ICC before and after resection were developed based on the final step of the multivariable logistic regression model. Specifically, the β coefficients of the risk factors of VER identified in the final step of the respective multivariable logistic regression models were used to construct a weighted composite preoperative and postoperative score. Estimated probabilities of developing VER were calculated according to the following formula: $P = 1/\{1+\exp[-(\text{Preoperative or Postoperative Score})]\}$, in which P is the probability of developing VER. For the multivariable logistic regression analysis, multivariate normal imputations were performed for missing data.[20] By using the X-tile program,[21,22] the optimal cutoffs of pre- and postoperative risk scores were determined to stratify patients at low, intermediate, or high risk for VER.[23] In addition, a model using discrete categorical variables was developed. In this model, the hazard ratio (HR) of factors that were significant in the multivariable model was assigned discrete points to create a simple scoring system, as previously reported.[24] Differences in recurrence-free survival (RFS) or OS between different subgroups of patients were assessed using the Kaplan-Meier method and the log-rank test.

To assess the performance of the prognostic model, the C index was calculated for the entire data set (training data set) as well as with the bootstrapping resample method (n = 5000) (internal validation). Calibration of the models was performed by plotting the predicted probabilities against the observed outcomes of the cohort. The accuracy of the prognostic model to predict VER was also externally validated using data from the Cleveland Clinic (Cleveland, Ohio) and the First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China). Because of data collection limitations, only the postoperative VER model was externally validated. The level of statistical significance was set at $\alpha = .05$. To account for the possible association of a period effect, additional sensitivity analyses were also performed after excluding patients who underwent liver resection before 2000. All statistical analyses were performed using SPSS, version 25 (IBM), along with JMP statistical package, version 14 (SAS Institute).

Results

Patient Characteristics With or Without VER

A total of 880 patients met the inclusion criteria and were included in the final analytic cohort (**Table 1**). The median patient age was 59 years (IQR, 51-68 years), 491 patients (55.9%) were men, and 562 (70.4%) had an American Society of Anesthesiologists class of 2 or lower. Most patients underwent a major hepatectomy (491 [56.9%]) for a T1 or T2 tumor (708 [84.0%]); a subset of patients had LN metastases (165 [18.8%]). Approximately one-third of patients received adjuvant chemotherapy or radiotherapy (279 [32.7%]) (Table 1). Overall, 196 patients (22.3%) had VER, whereas 684 (77.7%) did not (non-VER group); 374 patients (42.5%) had a recurrence more than 6 months after resection and 310 patients (35.3%) did not experience a recurrence during the follow-up period. Differences in the characteristics of patients with and without VER are summarized in Table 1.

Survival and Risk Factors of Patients With VER

After a median follow-up time of 24.1 months (IQR, 13.2-43.6 months), the median and 5-year OS among patients with and without VER was 13.8 months (IQR, 11.6-15.3 months) and 8.9% vs 59.7 months (IQR, 48.2-73.8 months) and 49.8%, respectively ($P < .001$) (**Figure 1**). On multivariable analysis of preoperative factors, race of color (odds ratio [OR], 1.79; 95% CI, 1.23-2.60), liver cirrhosis (OR, 2.06; 95% CI, 1.25-3.40), larger tumor size (OR, 1.12; 95% CI, 1.06-1.17), higher number of tumors (OR, 1.36; 95% CI, 1.15-1.60), and suspicious/metastatic LNs on preoperative imaging (OR, 1.90; 95% CI, 1.28-2.84) remained associated with a higher likelihood of VER, whereas higher age was associated with lower odds of VER (OR, 0.97; 95% CI, 0.96-0.99) (**Table 2**). A separate multivariable analysis that included all pre- and postoperative factors demonstrated that race of color (OR, 2.04; 95% CI, 1.38-3.00), larger tumor size (OR, 1.11; 95% CI, 1.06-1.17), higher number of tumors (OR, 1.36; 95% CI, 1.15-1.60), microvascular invasion (OR, 1.55; 95% CI, 1.06-2.26), N1 or Nx disease (OR, 1.94; 95% CI, 1.29-2.94), and R1 resection (OR, 2.14; 95% CI, 1.27-3.60) were each associated with greater odds of VER, whereas older age was again associated with lower odds of VER (OR, 0.97; 95% CI, 0.95-0.98) (Table 2). Neither hospital location (Eastern vs Western: OR, 1.33; 95% CI, 0.77-2.30) nor year of surgery (OR, 0.96; 95% CI, 0.92-1.02) were associated with VER. A sensitivity analysis after excluding patients who underwent rerersection of a recurrent tumor (total number of patients analyzed, 870 [98.9%]) revealed the same variables were associated with VER, with only slightly changed ORs compared with the aforementioned models (eTable 1 in the Supplement).

Development of Preoperative and Postoperative Risk Scores to Predict VER

Pre- and postoperative risk scores were developed based on the factors identified in the respective multivariable models (Table 2). Subsequently, patients were categorized into 3 different risk categories for VER based on the preoperative risk score: low risk (455 [51.7%]; 6-month RFS, 87.7%), intermediate risk (332 [37.7%]; 6-month RFS, 72.3%), and high risk (93 [10.6%]; 6-month RFS, 49.5%) ($P < .001$) (Table 2 and **Figure 2**A). Similarly, patients were categorized into 3 different risk groups for VER based on the postoperative risk score: low risk (440 [50.0%]; 6-month RFS, 90.0%), intermediate risk (308 [35.0%]; 6-month RFS, 73.1%), and high risk (132 [15.0%]; 6-month RFS, 48.5%) ($P < .001$) (Table 2 and Figure 2B). To facilitate clinical applicability of the preoperative and postoperative models, a convenient online calculator able to calculate the probability of VER and the risk group of VER assigned on the basis of the pre- and postoperative scores was devel-

Table 1. Comparison of Baseline Characteristics and Operative Variables Between Patients With and Without Very Early Recurrence Within 6 Months After Curative-Intent Liver Resection for Intrahepatic Cholangiocarcinoma

Variables	No. (%)			*P* value
	Total (N = 880)	VER (n = 196)	Non-VER (n = 684)	
Age, median (IQR), y	59 (51-68)	55.0 (47-63)	61.0 (52-69)	<.001
Sex				
Men	491 (55.9)	115 (58.7)	376 (55.1)	.41
Women	388 (44.1)	81 (41.3)	307 (45.0)	
Race				
White	428 (50.2)	76 (39.8)	352 (53.3)	.007
Asian	377 (44.3)	107 (56.0)	270 (40.9)	
Black	27 (3.2)	5 (2.6)	22 (3.3)	
Other	20 (2.3)	3 (1.6)	17 (2.6)	
BMI, median (IQR)	25 (22.1-27.7)	25.0 (22.5-28.5)	25.0 (22.1-27.6)	.53
Liver cirrhosis	95 (12.3)	33 (19.4)	62 (10.3)	.002
ASA				
≤2	562 (70.4)	135 (73.8)	427 (69.4)	.27
>2	236 (29.6)	48 (26.2)	188 (30.6)	
CA 19-9, median (IQR), UI/mL	48.0 (17.8-215.0)	60.9 (26.0-322.0)	44.8 (16.3-182.7)	.008
CEA, ng/mL	2.4 (1.5-4.3)	2.8 (1.5-5.3)	2.4 (1.5-3.8)	.03
LNM on imaging				
Negative	706 (80.2)	143 (73.0)	563 (82.3)	.006
Suspicious or positive	174 (19.8)	53 (27.0)	121 (17.7)	
Tumor size, median (IQR), cm	6.0 (4.0-8.3)	7.0 (5.2-9.5)	5.8 (3.9-8.0)	<.001
Multiple lesions (≥2)	140 (16.2)	49 (25.3)	91 (13.5)	<.001
Bilobar tumor	147 (17.0)	33 (17.1)	114 (17.0)	>.99
Macrovascular invasion	100 (11.4)	23 (11.7)	77 (11.3)	.90
Microvascular invasion	234 (26.6)	65 (33.2)	169 (24.7)	.02
Perineural invasion	136 (17.0)	23 (12.6)	113 (18.3)	.07
AJCC tumor category				
T1	389 (44.9)	52 (27.8)	314 (50.0)	<.001
T2	319 (39.1)	105 (56.2)	214 (34.1)	
T3	96 (11.8)	18 (9.6)	78 (12.4)	
T4	34 (4.2)	12 (6.4)	22 (3.5)	
AJCC node category				
N0	270 (30.7)	42 (21.4)	228 (33.3)	<.001
N1	165 (18.8)	52 (26.5)	113 (16.5)	
Nx	445 (50.6)	102 (52.0)	343 (50.2)	
Histological type				
Well to moderate	695 (83.3)	151 (83.0)	544 (83.4)	.12
Poorly to undifferentiated	139 (16.7)	31 (17.0)	108 (16.6)	
Morphological type				
MF, IG	738 (88.8)	162 (85.7)	576 (89.7)	.15
PI, MF + PI	93 (11.2)	27 (14.3)	66 (10.3)	
Resection procedure				
Minor	372 (43.1)	91 (47.2)	281 (41.9)	.22
Major	491 (56.9)	102 (52.9)	389 (58.1)	
R1 resection	105 (11.9)	32 (16.3)	73 (10.7)	.03
Intraoperative blood loss, median (IQR), ml	400 (200-750)	400 (200-800)	400 (200-750)	.77
Duration of surgery, median (IQR), min	200 (120-316)	173 (116-300)	200 (120-335)	.04
Adjuvant chemotherapy/radiotherapy	279 (32.7)	56 (29.8)	223 (33.5)	.38
Postoperative complications	316 (36.3)	65 (33.7)	251 (37.0)	.45

Abbreviations: AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CA, carbohydrate antigen; CEA, carcinoembryonic antigen; IG, intraductal growth; IQR, interquartile range; LNM, lymph node metastasis; MF, mass forming; PI, periductal infiltrating; VER, very early recurrence.

SI conversion factor: To convert CEA to µg/L, multiply by 1.

oped (eFigure 1 in the Supplement), which is available at: https://k-sahara.shinyapps.io/Veryearly-recurrence/.

Predictive Performance of the Models to Predict VER

The discriminative accuracy of the preoperative model was very good in the training data set (C index: 0.710; 95% CI, 0.666-0.750) and the validation data set with bootstrapping resamples (C index: 0.715; 95% CI, 0.700-0.730). Similarly, the predictive accuracy of the postoperative model was very good in the training data set (C index: 0.722; 95% CI, 0.677-0.759) as well as the validation data set with bootstrapping resamples (C index: 0.728; 95% CI, 0.715-0.742). The calibration plots demonstrated overall good agreement between the estimated probability of VER and the observed frequency of VER in the pre- and postoperative models (**Figure 3**). A sensitivity analysis was conducted that included only patients who underwent surgery after 2000 (eTable 2 in the Supplement). The differences in the predicted probability of VER were minor (0.6% in the pre- and post-operative models).

The postoperative VER model performed well in the external validation cohort (C index: 0.672; 95% CI, 0.595-0.742). Specifically, patients deemed high risk had a worse RFS compared with patients who were either intermediate or low risk for VER (6-month RFS: low risk, 80.4% vs intermediate risk, 75.3% vs high risk, 44.4%; $P < .01$) (eFigure 2 and eTable 3 in the Supplement).

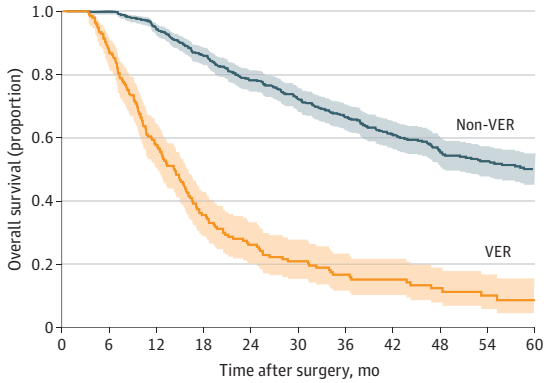
Development and Validation of a Simple Scoring System

A simple discrete scoring system was also developed to facilitate prognostic classification of patients without the need of the online calculator (eTable 4 in the Supplement). Specifically, patients with a preoperative score of 0 to 3, 4 to 5, and 6 to 9 had incrementally worse 6-month RFS (90.1% vs 75.6% vs 55.2%; $P < .001$; eFigure 3 in the Supplement). Similarly, based on the postoperative scoring system, patients with a score of 0 to 4, 5 to 6, and 7 to 10 had an incrementally worse 6-month RFS (91.1% vs 82.4% vs 57.7%; $P < .001$; eFigure 3 in the Supplement); this discrete postoperative scoring system was also able to stratify patient prognosis in the external validation cohort (6-month RFS: score of 0-4, 84.3% vs score of 5-6, 72.0% vs score of 7-10, 56.2%; $P < .001$) (eFigure 4 in the Supplement). The predictive accuracy of the pre- and postoperative models based on the scoring system was also very good in the training (C index: preoperative, 0.716; postoperative, 0.726) as well as the internal (C index: preoperative, 0.716; postoperative, 0.725; bootstrapping resamples, n = 5000) and external (C index: postoperative, 0.692) validation data sets.

Treatment and Outcomes of Patients With VER

Among 196 patients who had VER, most had intrahepatic recurrence only (117 [60.3%]); a subset had extrahepatic recurrence (29 [15.0%]) or intra- and extrahepatic recurrence (48 [24.7%]). Among patients with VER, only 10 patients (5.1%) underwent reresection compared with 45 individuals (12.0%) among those who experienced a later recurrence ($P < .001$), and most received the best supportive care (100 [51.0%]) (eTable 5 in the Supplement). The median OS following VER was 9.3 months (95% CI, 8.0-10.5 months). Three-year OS after recurrence was better among patients who underwent reresection vs individuals who received other types of treatment (54.0% vs 13.0%; $P = .001$) (eFigure 5 in the Supplement).

Figure 1. Kaplan-Meier Curve Demonstrating the Differences in Overall Survival Between Patients With and Without Very Early Recurrence (VER)



No. at risk											
Non-VER	684	677	584	484	398	325	270	218	165	134	115
VER	196	166	103	57	42	33	23	18	11	9	7

Discussion

Several previous studies have used the term *VER* to characterize recurrence within 6 months following resection for HCC and colorectal liver metastases.[14-16] Although there is no consensus about the exact timing of early recurrence among patients with ICC, using a cutoff of 2 years for ICC may be problematic because many patients with ICC have recurrence much earlier within the very first months following resection.[5] This study demonstrated that approximately one-fourth of patients (22.3%) developed recurrence within 6 months after resection for ICC. Patients with a VER had a median OS as low as 13.8 months, which is similar to patients with advanced cholangiocarcinoma who received systemic chemotherapy in a phase 3 randomized clinical trial (median OS, 11.7 months).[25] In addition, 2 models, one preoperative and one postoperative, were developed to calculate the risk of VER among patients with resectable ICC. Using the preoperative model, patients were categorized into low- (455 [51.7%]), intermediate- (332 [37.7%]), and high-risk groups (93 [10.6%]) with an incrementally worse 6-month RFS (87.7% vs 72.3% vs 49.5%; $P < .001$). Similarly, a postoperative model identified 3 groups of patients with an incrementally worse RFS (6-month RFS: 90.0% vs 73.1% vs 48.5%; $P < .001$). Using an online calculator developed in this study, physicians can calculate the individualized possibility of patients to develop VER in the pre- and postoperative setting. An additional simple discrete scoring system to predict VER was developed and validated that can be used by physicians without requiring the use of an online calculator. To our knowledge, this is the first study to define the incidence and risk of VER as well as provide a prediction tool to assess the likelihood of VER among patients undergoing surgery for ICC.

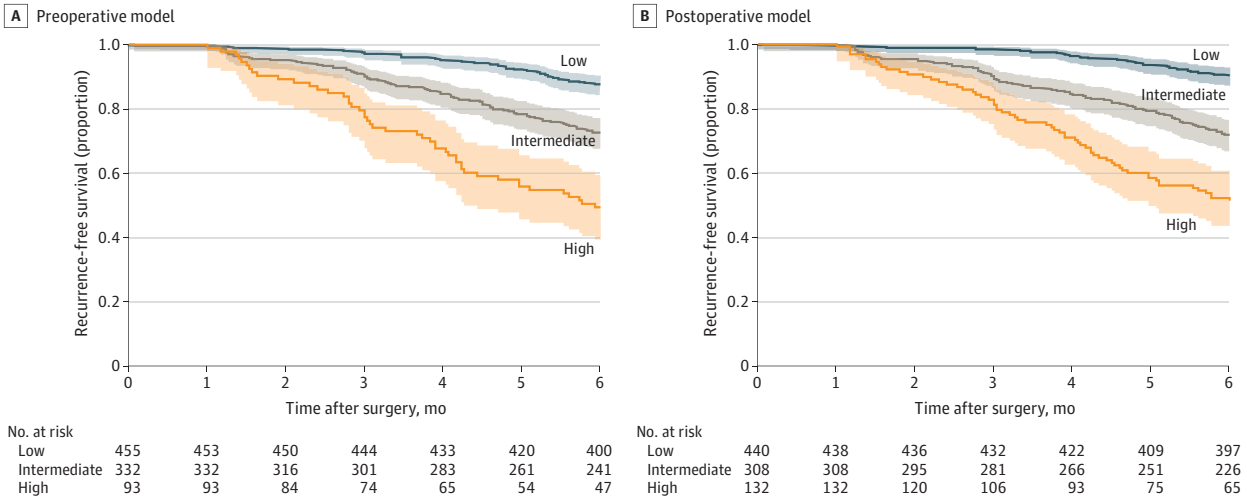
Table 2. Bivariate and Multivariable Logistic Regression Analyses of Factors Associated With Very Early Recurrence in Patients Who Underwent Curative-Intent Liver Resection of Intrahepatic Cholangiocarcinoma[a]

			Multivariable analysis			
	Bivariate analysis		Preoperative model		Postoperative model	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	0.96 (0.95-0.98)	<.001	0.97 (0.96-0.99)	<.001	0.97 (0.95-0.98)	<.001
Race						
White	1 [Reference]	NA	1 [Reference]	.002	1 [Reference]	<.001
Person of color	1.70 (1.23-2.34)	.001	1.79 (1.23-2.60)		2.04 (1.38-3.00)	
Liver cirrhosis	2.03 (1.29-3.21)	.002	2.06 (1.25-3.40)	.005	NA	
Ln CA19-9	1.11 (1.02-1.22)	.02	NA			
Tumor size (cm)	1.10 (1.06-1.15)	<.001	1.12 (1.06-1.17)	<.001	1.11 (1.06-1.17)	<.001
No. of lesions	1.37 (1.18-1.58)	<.001	1.36 (1.15-1.60)	<.001	1.36 (1.15-1.60)	<.001
Microvascular invasion	1.51 (1.07-2.13)	.02	NA	NA	1.55 (1.06-2.26)	.03
LNM on imaging						
No	1 [Reference]	.004	1 [Reference]	.002	NA	NA
Suspicious or positive	1.72 (1.19-2.50)		1.90 (1.28-2.84)			
AJCC N category						
N0	1 [Reference]	NA	NA	NA	1 [Reference]	NA
N1 or Nx	1.83 (1.26-2.67)	.001			1.94 (1.29-2.94)	.001
R1 margin	1.63 (1.04-2.56)	.03			2.14 (1.27-3.60)	.005

Abbreviations: AJCC, American Joint Committee on Cancer; Ln, natural logarithm; LNM, lymph node metastasis.

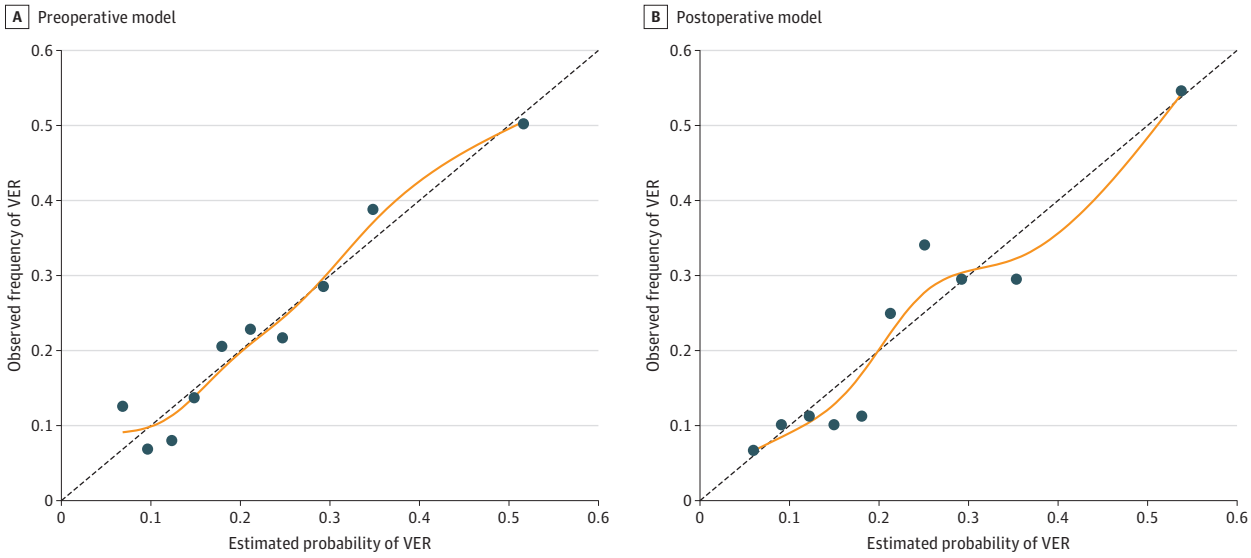
[a] Prescore = 1.911 − 0.030 × Age + 0.581 × (Race, Nonwhite: 1; White: 0) + 0.724 × (Cirrhosis: Yes: 1; No: 0) + 0.111 × Size (cm) +0.304 × Number of Lesions +0.643 × (LNM on Imaging Suspicious or Positive: 1, Negative: 0). For the determination of cutoffs based on the prescore, please use: low, 1.77 or less; intermediate, more than 1.77 to 2.69 or less; high, more than 2.69. Postscore = 1.811 − 0.032 × Age + 0.711 × (Race: Nonwhite, 1; White, 0) + 0.104 × Size (cm) + 0.307 × Number of Lesions + 0.665 × (N Stage N1 or Nx: 1; N0: 0) + 0.436 (Microvascular Invasion: Yes, 1; No, 0) + 0.759 (Surgical Margin: R1, 1; R0, 0). For the determination of cutoffs based on the postscore, please use: low, 2.02 or less; intermediate, more than 2.02 to 2.80 or less; and high, more than 2.80.

Figure 2. Kaplan-Meier Curves Demonstrating the Differences in Recurrence-Free Survival Among Low-, Intermediate-, and High-Risk Patients for Very Early Recurrence Based on the Preoperative and Postoperative Models



This study developed 2 models to predict VER following resection for ICC. Based on variables, such as age, race, liver cirrhosis, tumor size and number, and radiologic LN status, the preoperative model was able to identify 3 groups of patients with different risk for VER (ie, low-, intermediate-, and high-risk groups) who had an incrementally worse 6-month RFS (87.7% vs 72.3% vs 49.5%; $P < .001$) (Figure 2A). Incorporating pathologic data, including microvascular invasion, nodal status, and resection margins, the postoperative model was able to stratify patients according to risk for VER (90.0% vs 73.1% vs 48.5%; $P < .001$). Tumor size and number (eg, tumor burden),[26] microvascular and nodal invasion,[6] liver cirrhosis, and resection margins have been associated with risk of recurrence among patients with

Figure 3. Calibration Plots for the Preoperative and Postoperative Models Associated With the Prediction of Very Early Recurrence (VER)



The dots represent the deciles of patients' observed frequency of VER plotted against the estimated/predicted probability of VER. The smooth lines are cubic splines representing the relationship between the frequency and the predicted probability of VER.

ICC.[10,27] In contrast, data on age as a predictor of outcomes among patients with cancer have been more equivocal.[3,28] In this study, younger age remained associated with a higher chance for VER in the pre- and postoperative models. Although the explanation is likely multifactorial, the increased proliferative and angiogenic activity of tumor cells in younger individuals may be significantly associated with recurrence rates.[29] The presence of cirrhosis was only included in the preoperative predictive model; the former did not remain associated with VER after accounting for other variables available during the postoperative period (eg, vascular invasion). In addition, suspicious or metastatic LNs on preoperative imaging were replaced in the postoperative model with actual pathologic nodal status. Taken together, the data highlight how patients with multiple nodules, large tumor size, and suspicious or metastatic LNs on preoperative imaging have a markedly higher likelihood of experiencing VER and, in turn, a poor survival.[11] Thus, identifying patients who are likely to experience a VER is particularly important because these patients should be considered for clinical trials, neoadjuvant therapy, or other nonsurgical treatment modalities. In addition, characterizing patients at risk for VER in the postoperative setting may be useful in determining the intensity of the surveillance strategy, as well as identifying patients who might benefit more from adjuvant chemotherapy following resection of ICC.

The finding that 1 in 4 patients experienced VER with an overall survival of roughly 1 year after surgery was particularly notable. These data were comparable with outcomes among many patients with pancreatic adenocarcinoma who often have recurrence early and have a very poor survival rate.[30] Because of these poor outcomes, there has been a marked increase over the last decade in the routine use of neoadjuvant chemotherapy among patients with pancreatic cancer.[31] Neoadjuvant therapy is used for many reasons, including early treatment of micrometastatic disease, in addition to treatment of the index lesion.[32] In this manner, early systemic chemotherapy provides a therapeutic and selection role to help determine which patients may benefit most from an attempt at curative-intent surgery.[33] In fact, neoadjuvant therapy has been demonstrated to be effective in increasing disease-free survival among patients with pancreatic and perihilar cholangiocarcinoma.[34,35] Despite this, the use of neoadjuvant therapy among patients with ICC remains extremely low.[36] However, more recently, epidermal growth factor receptor signaling pathway, as well as isocitrate dehydrogenase mutations, have been identified as specific therapeutic targets for systemic therapy.[37,38] Therefore, use of the VER tool may be important to inform a potential paradigm shift in treating patients with ICC. Specifically, by using the tool proposed in this study (https://k-sahara.shinyapps.io/Veryearly-recurrence/), surgeons can estimate the individualized risk of a specific patient to experience VER. In addition, by using the simple scoring system developed in this study, physicians can also estimate the risk of VER without requiring the use of an online calculator (eTable 4 and eFigures 3 and 4 in the Supplement). In turn, patients at high risk for VER should be considered candidates for clinical trials, neoadjuvant systemic chemotherapy, or alternative liver-directed treatment options rather than upfront surgery.

Limitations

Several limitations should be considered when interpreting the results of this study. While the multi-institutional nature of the database was a strength, there may have been some heterogeneity in patient selection and surgical techniques among the different participating centers. The dura-

tion of the cohort may have also contributed to a period effect and associated heterogeneity; however, a sensitivity analysis that excluded patients who underwent an operation before 2000 (n = 33) demonstrated similar results. In addition, data on CA19-9 levels 1 month after surgery were not available in the data set and we were thus unable to assess whether this information could predict VER following liver resection of ICC. However, not all patients with ICC express CA19-9 and the more comprehensive postoperative model developed in the context of this study did predict VER well in the test and external validation cohorts. Information on α-fetoprotein levels was also not available in the database because most centers routinely measure CA19-9 and not α-fetoprotein for ICC patients; all patients underwent resection for pure ICC and none had mixed HCC-ICC. Furthermore, there may have been slight variations in radiologic or pathologic assessment of tumor size and number at different centers depending on the method of assessment; however, these are unlikely to be clinically significant.[23]

Conclusions

Approximately one-fourth of patients undergoing curative-intent hepatectomy for ICC developed VER, which was associated with a very discouraging prognosis. An easy-to-use online calculator to predict the risk of VER was developed based on clinicopathological variables available before and after resection for ICC. The VER calculator demonstrated a very good accuracy on internal and external validation. The online calculator may help clinicians to use neoadjuvant therapy more often among high-risk patients with ICC as well as inform the intensity of surveillance following resection.

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